## AMENDMENTS TO THE SPECIFICATION

On page 31, beginning at line 5 at page 31 until page 31 at line 15, please amend as follows:

--The following discussion is provided to illustrate the algorithm using exemplary data. In this example, eight test peptides are selected from a tetrapeptide library: ~~DKAH~~ Asp-Lys-Ala-His (SEQ. ID. NO:23), ~~DWPA~~ Asp-Trp-Pro-Ala (SEQ. ID. NO:24), ~~ESMH~~ Glu-Ser-Met-His (SEQ. ID. NO:25), ~~GVNE~~ Gly-Val-Asn-Glu (SEQ. ID. NO:26), ~~HEDV~~ His-Glu-Asp-Val (SEQ. ID. NO:27), ~~ETGS~~ Glu-Thr-Gly-Ser (SEQ. ID. NO:28), ~~HYGV~~ His-Tyr-Gly-Val (SEQ. ID. NO:29, and ~~DFGV~~ Asp-Phe-Gly-Val (SEQ. ID. NO:30)~~(SEQ ID NO:23 to SEQ ID NO:30~~; **Table 3**). The test peptides may be selected from the library by any means known in the art. The values for three parameters (molecular weight, total charge, and mlogp, *i.e.*, hydrophobicity) may be determined for each of the eight peptides. The indicia of the property, in this example a particular biological activity (*i.e.*, protein production), may be determined for the eight peptides as well. The exemplary data are shown in **Table 3**.

**Table 3**

| SEQ ID NO: | Peptide | Hydro-phobicity | Mol. Wt | Total Charge | Biol. Act. |
|---|---|---|---|---|---|
| 23 | ~~DKAH~~Asp-Lys-Ala-His | -3.479 | 469.499 | 0 | 15.0 |
| 24 | ~~DWPA~~Asp-Trp-Pro-Ala | -1.608 | 486.505 | -1 | 25.0 |
| 25 | ~~ESMH~~Glu-Ser-Met-His | -3.479 | 501.535 | -1 | 19.3 |
| 26 | ~~GVNE~~Gly-Val-Asn-Glu | -3.421 | 416.411 | -1 | 14.4 |
| 27 | ~~HEDV~~His-Glu-Asp-Val | -4.03 | 496.477 | -2 | 18.5 |
| 28 | ~~ETGS~~Glu-Thr-Gly-Ser | -4.25 | 391.357 | -1 | 10.2 |

| | | | | | |
|---|---|---|---|---|---|
| 29 | ~~HYGV~~His-Tyr-Gly-Val | -1.278 | 474.518 | 0 | 23.6 |
| 30 | ~~DFGV~~Asp-Phe-Gly-Val | -1.616 | 435.457 | -1 | 22.0 |

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On page 32, beginning at line 5 ending at line 8 on page 33, please amend as follows:

--If a satisfactory peptide (*i.e.*, satisfies the test requirement) is not identified among the first set of test peptides, the screening process will continue. A second set of untested peptides can then be selected by any means known in the art, and the parameter for the second set of peptides may be calculated. Using Equation 1, the predicted activity of a second set of culture media, where each of the culture media in the set contains one of the second test peptides, can be calculated for each culture media in the second set based on the parameters of the peptide included therein. For example, a predicted activity of 28.2 was derived for a culture medium containing the untested peptide ~~HYPV~~ His-Tyr-Pro-Val (SEQ ID NO: 31; **Table 4**). This value is higher than any of the biological activities in the original library, and, thus, this peptide would be a good candidate for synthesis and testing.

**Table 4**

| Predicted Peptide | Hydro-phobicity | Mol. Wt | Total Charge | Predicted Biol. Act. |
|---|---|---|---|---|
| ~~HYPV~~ His-Tyr-Pro-Val (SEQ ID NO:31) | -0.645 | 514.583 | 0 | 28.2 |

If the test requirement is for protein production at a level of at least 25, then the compound screening process may end with the identification of ~~HYPV~~ His-Tyr-Pro-Val (SEQ ID NO:31) (assuming the actual biological activity is equal to the predicted activity). Alternatively, if the test requirement is set for protein production of at least 30, then the screening process would continue. The actual indicia of the property of a second set of culture media, each containing one of the second test peptides, may be determined. From these

measurements, a new relationship between at least one parameter and biological activity is calculated. From this updated equation, a third set of peptides, which when included in culture media are predicted to promote protein production by the bacteria at a level of 30 or greater are identified. Typically, this process can continue in an iterative fashion until a peptide having the desired biological activity is identified.

Likewise, if the test requirement was set at a level of at least 20, then three of the original test peptides would satisfy the test requirement (*e.g.*, ~~DWPA~~Asp-Trp-Pro-Ala (SEQ. ID. NO:24), ~~HYGV~~ His-Tyr-Gly-Val (SEQ. ID. NO:29), and ~~DFGV~~ Asp-Phe-Gly-Val (SEQ. ID.NO:30); ~~SEQ ID NO:24, SEQ ID NO:29, and SEQ ID NO:30, respectively;~~ **Table 3**), and the compound screening process could stop at this point or could continue to look for even better performing peptides.--

On page 35, beginning at line 4 and ending at line 6 on page 39, please amend as follows:

--According to this illustrative example, the present invention can be used to identify a peptide as a culture medium component, *e.g.*, for mammalian hybridoma cells producing and secreting antibodies. In particular, it is desirable to identify peptides, which when added to culture medium, will promote antibody production by hybridoma cells at a level greater than a test requirement. Four test peptides (~~DKAH~~Asp-Lys-Ala-His (SEQ. ID NO:23), ~~DWPA~~Asp-Trp-Pro-Ala (SEQ. ID NO:24), ~~ESMH~~Glu-Ser-Met-His (SEQ. ID NO:25), ~~GVNE~~Gly-Val-Asn-Glu (SEQ. ID NO:26); ~~SEQ ID NO:23 to SEQ ID NO:26,~~ *i.e.*, a training set) may be selected from a peptide library as described above with respect to the QSAR example. Values to describe the various parameters of the peptides, for example, hydrophobicity (*i.e.*, mlogp), molecular weight, and total charge may be calculated for each peptide (**Table 5**). Each peptide may be added to hybridoma culture medium and antibody production (*i.e.*, biological activity) may be measured for the cells cultured in each culture medium (values shown in **Table 5**).

**Table 5**

| SEQ ID NO: | Peptide | Hydro-phobicity | Mol. Wt | Total Charge | Biol. Act. |
|---|---|---|---|---|---|
| 23 | ~~DKAH~~ Asp-Lys-Ala-His | -3.479 | 469.499 | 0 | 15.0 |
| 24 | ~~DWPA~~Asp-Trp-Pro-Ala | -1.608 | 486.505 | -1 | 25.0 |
| 25 | ~~ESMH~~Glu-Ser-Met-His | -3.479 | 501.535 | -1 | 19.3 |
| 26 | ~~GVNE~~Gly-Val-Asn-Glu | -3.421 | 416.411 | -1 | 14.4 |

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Assume that there is a second set of untested (*i.e.*, candidate) peptides as shown in **Table 6**.

**Table 6**

| SEQ ID NO: | Peptide | Hydro-phobicity | Mol. Wt | Total Charge | Biol. Act. |
|---|---|---|---|---|---|
| 27 | ~~HEDV~~His-Glu-Asp-Val | -4.03 | 496.477 | -2 | ? |
| 28 | ~~ETGS~~Glu-Thr-Gly-Ser | -4.25 | 391.357 | -1 | ? |
| 29 | ~~HYGV~~His-Try-Gly-Val | -1.278 | 474.518 | 0 | ? |
| 30 | ~~DFGV~~Asp-Phe-Gly-Val | -1.616 | 435.457 | -1 | ? |

The idea of the nearest neighbor rule is to find candidate peptides with parameters that are similar to those from the peptide(s) with the "best" (in this case highest) observed biological activity or the lead peptide(s). Before performing any calculations, typically all parameters will be standardized so that they will each have an equal contribution to the nearest neighbor calculation. In this illustrative example, all parameters may be standardized so that they lie between the values of 0 and 1. This standardization ensures that all parameters will have an equal contribution to the nearest neighbor calculation. A standardized value may be computed in the following manner:

Standardized value = (Original value – Min. value)/ (Max. value – Min. value) **(2)**

For example the standardized value of molecular weight for the peptide ~~DKAH~~ Asp-Lys-Ala-His (SEQ ID NO:23) may be calculated as follows:

(469.499 - 391.357)/(501.535 - 391.357) = 0.7092 **(3)**

The standardized parameter values for the eight peptides are displayed below in **Table 7**.

**Table 7**

| SEQ ID -NO: | Peptide | Hydrophobicity | Molecular Weight | Total Charge |
|---|---|---|---|---|
| 23 | ~~DKAH~~ Asp-Lys-Ala-His | 0.2594 | 0.7092 | 1 |
| 24 | ~~DWPA~~Asp-Trp-Pro-Ala | 0.889 | 0.8636 | 0.5 |
| 25 | ~~ESMH~~Glu-Ser-Met-His | 0.2594 | 1 | 0.5 |
| 26 | ~~GVNE~~Gly-Val-Asn-Glu | 0.2789 | 0.2274 | 0.5 |
| 27 | ~~HEDV~~His-Glu-Asp-Val | 0.074 | 0.9541 | 0 |
| 28 | ~~ETGS~~Glu-Thr-Gly-Ser | 0 | 0 | 0.5 |
| 29 | ~~HYGV~~His-Tyr-Gly-Val | 1 | 0.7548 | 1 |
| 30 | ~~DFGV~~Asp-Phe-Gly-Val | 0.8863 | 0.4003 | 0.5 |

Once the standardized values have been calculated, nearest neighbors may be determined by calculating the Euclidean distances between the peptides in this 3-dimensional space (where 3 represents the number of parameters). For example, the distance between ~~DKAH~~ Asp-Lys-Ala-His (SEQ ID NO:23) and ~~HYGV~~ His-Tyr-Gly-Val (SEQ ID NO:29) is calculated as:

$$\text{SQRT}( (.2594 - 1)^2 + (.7092 - .7548)^2 + (1-1)^2) = .7420 \qquad \textbf{(4)}$$

**Table 8** contains these calculated distances between the training set of peptides and the candidate set of peptides.

**Table 8**

| | | ~~HEDV~~His-Glu-Asp-Val | ~~ETGS~~Glu-Thr-Gly-Ser | ~~HYGV~~His-Tyr-Gly-Val | ~~DFGV~~ Asp-Phe-Gly-Val |
|---|---|---|---|---|---|
| SEQ ID NO:23 | ~~DKAH~~ Asp-Lys-Ala-His | 1.0461 | .9057 | .7420 | .8593 |
| SEQ ID NO:24 | ~~DWPA~~Asp-Trp-Pro-Ala | .9604 | 1.2394 | .5236 | .4633 |
| SEQ ID NO:25 | ~~ESMH~~Glu-Ser-Met-His | .5362 | 1.0331 | .9266 | .8675 |
| SEQ ID NO:26 | ~~GVNE~~Gly-Val-Asn-Glu | .9056 | .3599 | 1.0238 | .6315 |

The peptides in the candidate set will then be assigned predicted indicia of the property based the closest peptide in the training set (**Table 9**). The (hypothetical) biological activities for these four peptides may then be measured as shown in **Table 9**.

**Table 9**

| **Candidate Peptide** | **Closest Peptide** | **Predicted Biol. Activity** | **Observed Activity** |
|---|---|---|---|
| ~~HEDV~~His-Glu-Asp-Val (SEQ ID NO:27) | ~~ESMH~~ Glu-Ser-Met-His (SEQ ID NO:25) | 19.3 | 18.5 |
| ~~ETGS~~ Glu-Thr-Gly-Ser (SEQ ID NO:28) | ~~GVNE~~Gly-Val-Asn-Glu (SEQ ID NO:26) | 14.4 | 10.2 |
| ~~HYGV~~His-Tyr-Gly- | ~~DWPA~~Asp-Trp- | 25.0 | 23.6 |

| | | | |
|---|---|---|---|
| Val<br>(SEQ ID NO:29) | Pro-Ala<br>(SEQ ID NO:24) | | |
| ~~DFGV~~Asp-Phe-Gly-Val<br>(SEQ ID NO:30) | ~~DWPA~~Asp-Trp-Pro-Ala<br>(SEQ ID NO:24) | 25.0 | 22.0 |

The test rule is to test candidate peptides that are similar to the best members from the first test library. Thus, in this example, ~~HYGV~~ His-Tyr-Gly-Val (SEQ ID NO:29) and ~~DFGV~~ Asp-Phe-Gly-Val (SEQ ID NO:30) may be synthesized and tested. If either or both of the peptides satisfy the test requirement, the compound screening process may be stopped at this point. Alternatively, if a compound has not yet been identified, or if additional compounds are desired, the process can be continued in an iterative fashion. As a further alternative, the selection and screening process can be continued using a different relationship, *e.g.*, a QSAR relationship as described above. Finally, as described above, if the first screening yields a suitable compound, it may not be necessary to engage in successive rounds of picking a library and screening additional test compounds.--